Paper No. 29

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte STEVEN C. CLARK, GORDON G. WONG,
PAUL SCHENDEL, AND JOHN MC COY

Appeal No. 2001-2308
Application No. 07/704,578

ON BRIEF

Before WILLIAM F. SMITH, MILLS, and GRIMES, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 28 and 29. Claims 28 and 29 read as follows:

[1] The Examiner's Answer was mailed on May 4, 1994. For reasons not clear from the record, the file was not forwarded to the Board until July 2001. In view of the delay in the case being forwarded to the Board, we have taken the case up for decision out of turn.

28. A pharmaceutical composition which comprises an effective amount of a polypeptide having the sequence:

Ala Pro Val Pro Pro Gly Glu Asp Ser Lys Asp Val Ala Ala Pro His Arg Gln Pro Leu Thr Ser Ser Glu Arg Ile Asp Lys Gln Ile Arg Tyr Ile Leu Asp Gly Ile Ser Ala Leu Arg Lys Glu Thr Cys Asn Lys Ser Asn MET Cys Glu Ser Ser Lys Glu Ala Leu Ala Glu Asn Asn Leu Asn Leu Pro Lys MET Ala Glu Lys Asp Gly Cys Phe Gln Ser Gly Phe Asn Glu Glu Thr Cys Leu Val Lys Ile Ile Thr Gly Leu Leu Glu Phe Glu Val Tyr Leu Glu Tyr Leu Gln Asn Arg Phe Glu Ser Ser Glu Glu Gln Ala Arg Ala Val Gln MET Ser Thr Lys Val Leu Ile Gln Phe Leu Gln Lys Lys Ala Lys Asn Leu Asp Ala Ile Thr Thr Pro Asp Pro Thr Thr Asn Ala Ser Leu Leu Thr Lys Leu Gln Ala Gln Asn Gln Trp Leu Gln Asp MET Thr Thr His Leu Ile Leu Arg Ser Phe Lys Glu Phe Leu Gln Ser Ser Leu Arg Ala Leu Arg Gln MET

in combination with a pharmaceutically acceptable vehicle, wherein said polypeptide is non-glycosylated.

29. A bacterially produced non-glycosylated protein substantially free of other protein and characterized by the amino acid sequence:

Ala Pro Val Pro Pro Gly Glu Asp Ser Lys Asp Val Ala Ala Pro His Arg Gln Pro Leu Thr Ser Ser Glu Arg Ile Asp Lys Gln Ile Arg Tyr Ile Leu Asp Gly Ile Ser Ala Leu Arg Lys Glu Thr Cys Asn Lys Ser Asn MET Cys Glu Ser Ser Lys Glu Ala Leu Ala Glu Asn Asn Leu Asn Leu Pro Lys MET Ala Glu Lys Asp Gly Cys Phe Gln Ser Gly Phe Asn Glu Glu Thr Cys Leu Val Lys Ile Ile Thr Gly Leu Leu Glu Phe Glu Val Tyr Leu Glu Tyr Leu Gln Asn Arg Phe Glu Ser Ser Glu Glu Gln Ala Arg Ala Val Gln MET Ser Thr Lys Val Leu Ile Gln Phe Leu Gln Lys Lys Ala Lys Asn Leu Asp Ala Ile Thr Thr Pro Asp Pro Thr Thr Asn Ala Ser Leu Leu Thr Lys Leu Gln Ala Gln Asn Gln Trp Leu Gln Asp MET Thr Thr His Leu Ile Leu Arg Ser Phe Lys Glu Phe Leu Gln Ser Ser Leu Arg Ala Leu Arg Gln MET

The examiner relies on the following references:

Hirano et al (Hirano) "Purification to homogeneity and Characterization of Human B-Cell Differentiation Factor (BCDF or BSFp-2)," Proc.Natl Acad.Sci Vol. 82. pp. 5490-5494 (1985)

Weissenbach et al (Weissenbach), "Two Interferon mRNAs in Human Fibroblasts: In Vitro Translation and Escherichia Coli Cloning Studies," Proc. Natl. Acad. Sci Vol. 77, pp. 7152-7156 (1980)

Gilbert et al. (Gilbert),		4,338,397	Jul. 6 1982
Kishimoto (Japanese Patent)	JP	61-115025	Jun 02, 1986

Zilberstein et al (Zilberstein), "Human Interferon-β_2: Is It An Interferon-Inducer?," The Interferon System Serono Symposia Vol. 24. pp. 73-83 (1985)

The examiner also relies upon three additional documents without providing bibliographic information; based on the file history, we deduce these to be:

Revel et al (Revel) (Great Britian)	2,063,882	Nov. 19, 1990
Clark et al (Clark)	4,675,285	Jun 23, 1987
Ingolia	4,559,302	Dec. 17, 1985

GROUNDS OF REJECTION[2]

1. Claims 28 and 29 stand rejected alternatively under 35 U.S.C. 102 or 35 U.S.C. 103 as anticipated or obvious. As evidence of anticipation or obviousness, the examiner cites Hirano, Weissenbach, or Zilberstein.

2. Claims 28 and 29 stand rejected under 35 U.S.C. 103. As evidence of obviousness, the examiner cites Hirano, Weissenbach, Zilberstein, Revel, or JP 115025A in view of Gilbert, Ingolia, or Clark.

We reverse.

[2] A final rejection of claim 28 under 35 U.S.C. §112, first paragraph (enablement) and 35 U.S.C. §101 (utility) was withdrawn in the examiner's answer.

Background

Interleukin-6 (IL-6) is a natural substance having many biological activities. Many different names have been given to the natural substance by researchers obtaining the protein from a variety of different sources: 26 KD protein, IFN-beta-2, BCDF, and BSF-2, for example (specification, page 2). A cDNA sequence encoding IL-6 was isolated from an HTLV-transformed T cell line (specification, page 12). The cDNA is 1.1 kb long, and contains an open reading frame of 636 nucleotides encoding a protein of 212 amino acids including a leader secretory sequence (specification, page 8). The invention at bar involves the protein sequence from amino acids 28 through 212 (specification, page 7, and Figure 1). The disclosure includes production of glycosylated IL-6 in mammalian cell lines. The protein produced in a mammalian cell line has an apparent molecular weight range of approximately 20 to 35 KD, indicative of glycosylation (e.g. specification, page 21). Importantly, the claims before us are limited to the nonglycosylated protein. Production of nonglycosylated IL-6 in bacterial cells is disclosed, for example, at specification pages 6, 7, 18-20.

Rather than recapitulating the arguments of appellant and examiner, we refer to pages 11-33 of the Brief for the appellant's position, and pages 4-15 of the Examiner's Answer for the examiner's position.

Rejection 1

Claims 28 and 29 stand rejected alternatively under 35 U.S.C. §102 or 35 U.S.C. §103 as anticipated by or obvious over Hirano, Weissenbach, or Zilberstein.

Under certain circumstances, the USPTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. For example, where the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the USPTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product[3]. However, the examiner bears the initial burden of providing facts and reasons to believe that the prior art products are identical or substantially identical to the claimed product.

Claim 28 requires a nonglycosylated protein in combination with a pharmaceutically acceptable vehicle. In reviewing the Examiner's Answer, nowhere do we find that the examiner has acknowledged and discussed this aspect of the invention. Failure to consider the subject matter of the claim as a whole constitutes legal error. Accordingly, all rejections of claim 28 are reversed.

Claim 29 requires a product made by a specific process which is a non-glycosylated protein having a specific amino acid sequence and is substantially free of other protein. We find that the examiner has not provided adequate reasons to believe

[3] In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977).

that the reference products are identical, or substantially identical, to the product as claimed.

Hirano describes a purified product designated "BCDF" containing two bands of protein, and speculates that the difference in molecular weights "is the result of post-translational modification or the formation of breakdown products." Appellants argue that without a comparison of the amino acid sequences of these protein species it is impossible to assume that a single protein is present. The examiner argues that the specific activity is an indication of a substantially pure protein and is sufficient to identify the protein. The examiner also argues that the amino acid sequence is inherent to the protein. However, we note that the reference relied upon by the examiner identified as JP 61-115025 discusses "BCDF" and lists Hirano as an inventor. In the Japanese patent, "BCDF" was made from a similar cell line and purified by the same procedure as reported in Hirano. The N-terminal sequence of "BCDF" is reported as
Pro Val Pro Pro Gly Glu Asp Ser Lys Asp Val Ala Ala which lacks the N-terminal Ala residue recited in the claimed protein. Viewing these references together, we find that the Japanese patent provides evidence that the protein(s) of Hirano do not necessarily meet the particular limitations of claim 29. In our view, these circumstances are such that the examiner needed to explain the discrepancy between the respective amino acid sequences and explain how Hirano suggests the particular claimed product. The examiner did not do so.

In regard to Weissenbach, we note that the reference teaches a method of inducing and fractionating mRNAs encoding an interferon activity, making a cDNA from the fractionated mRNA, partial cDNAs (of undisclosed sequence) encoding "Hu IFN-$2", a specific mRNA hybrid-selected by the cDNA, and an isolated protein made by in vitro translation of the mRNA (Figure 4, lanes 7-9). In vitro translation products are the only proteins disclosed in this publication. See figures 2 and 4. The translation products are not purified free of other proteins; at best, they are immunoprecipitated. It is not clear to us, and the examiner has not explained, how the translation products disclosed in this publication meet the claim limitation of "substantially free of other protein".

In regard to Zilberstein, the reference mentions a biochemical fractionation procedure which yields "IFN-$2" and preparation of antisera. However, the publication refers to an unpublished document for details. Thus, it is not clear whether the reference enables the fractionation procedure[4]. The reference also discloses a protein made by rodent cell lines transfected by human genes. Being rodent cells, the cells would not

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[4] See In re Payne, 606 F.2d 303, 314, 203 USPQ 245, 255 (CCPA 1979) ("References relied upon to support a rejection under 35 U.S.C. § 103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public. In re Brown, 51 CCPA 1254, 1259, 329 F.2d 1006, 1011, 141 USPQ 245, 249 (1964). An invention is not 'possessed' absent some known or obvious way to make it. In re Hoeksema, 55 CCPA 1493, 1500, 399 F.2d [sic 269]. 274, 158 USPQ 596, 601 (1968).") See also In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (To be enabling a disclosure must teach persons skilled in the art to make and use the claimed invention without undue experimentation.).

produce the nonglycosylated protein required by the claim. Thus, absent a fact-based explanation from the examiner, we conclude that the proteins disclosed in this publication do not meet the claim limitations.

In sum, we do not find that the examiner has provided sufficient reason to believe that any of the reference products are identical, or substantially identical, to the product of claim 29. Therefore we reverse this rejection.

Rejection 2

Claims 28 and 29 stand rejected as obvious over Hirano, Weissenbach, Zilberstein, Revel, or JP 115025A in view of Gilbert, Ingolia, or Clark. The examiner states that Hirano, Weissenbach, Zilberstein, and Revel do not specifically teach the amino acid sequence of the protein, and with the exception of Revel do not specifically teach the expression of IL-6 in a prokaryotic cell or the production of an nonglycosylated IL-6. The JP document discloses a purified protein, and an N-terminal sequence. The examiner argues that it would have been obvious to use the methods of Gilbert, Ingolia, and Clark for expression of an nonglycosylated protein, for the advantages of homogeneity, ease of handling, and low cost. We disagree.

In discussing obviousness in In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)(citations omitted):

> The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gate either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. . . . In other, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

In order to succeed in producing a protein by expression in a prokaryotic cell, one must necessarily obtain a nucleic acid that encodes the desired protein. Hirano provides no guidance in this regard. While JP 115025 does describe the amino acid sequence for a small segment of the desired protein, the N-terminal sequence is not the same as the N-terminal sequence of the product recited in the claims. Even if one of skill in the art were to succeed in obtaining a coding sequence based upon the information given, the examiner has not explained why it would have been obvious to add an alanine residue at the N-terminus of the sequence disclosed in the patent.

In contrast, Weissenbach, Zilberstein, and Revel do teach nucleic acids. Weissenbach teaches sucrose gradient fractionation of mRNA from superinduced fibroblasts, isolation of about 25 cDNA clones, selection of one clone A341, identification of 12 of the clones as having overlapping sequence, and identification of an mRNA of

1270+/-70 nucleotides as hybridizing to clone A341. Zilberstein in addition provides a restriction map for two genomic clones. Revel discusses how one would produce a cDNA, and mentions the desirability of bacterial expression. The examiner argues that Weissenbach and Zilberstein set forth sufficient information/direction to obtain the nucleotide sequence for the IFN-$2 DNA. However, these references provide little or no guidance related to the existence or nonexistence of a secretory leader sequence, or production of a mature protein. We note that the claims are not directed to IL-6 protein as it is encoded by the mRNA, but require the protein divested of its leader secretory sequence (see specification pages 7-8 and Figure 1). Even if these references provided sufficient guidance to produce full-length cDNAs and express the products encoded by the cDNAs, they provide no guidance or direction to the claimed product, which is lacking a signal sequence. Therefore combination of the teachings of these references with Gilbert, Ingolia or Clark would not lead to the claimed product. The only art teaching a particular N-terminal protein sequence is JP 115025A. This reference does not teach or suggest the same N-terminus as recited in the claim, and furthermore does not provide any reason to combine its teachings regarding a B-cell differentiation factor protein with the teachings of the interferon nucleic acids.

Therefore, we conclude that the cited references do not provide sufficient guidance or direction to lead one of ordinary skill in the art to the product as claimed, with a reasonable expectation of success.

REVERSED

William F. Smith	)
Administrative Patent Judge	)
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	)
	) BOARD OF PATENT
Demetra J. Mills	)
Administrative Patent Judge	) APPEALS AND
	)
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